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Thromboembolic and bleeding outcomes of low-intensity warfarin thromboprophylaxis following elective total hip arthroplasty

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ABSTRACT

Background: Low-intensity warfarin is among the most frequently prescribed thromboprophylaxis regimens after major orthopedic surgery in the United States. This has been a source of controversy as the American College of Chest Physicians historically recommended standard intensity warfarin (INR 2–3) over low-intensity warfarin in this setting. The updated guidelines include low-intensity warfarin as a recommended option, but data evaluating this intervention has not kept pace with newer agents.
Materials and Methods: We describe the risk of symptomatic venous thromboembolism and clinically relevant bleeding in a retrospective cohort of patients receiving low-intensity warfarin (INR 1.5 to 2.5) for six weeks after total hip arthroplasty. Outcomes were identified within a joint replacement registry and cross-verified by queries of electronic inpatient and outpatient databases and independently adjudicated by chart review.
Results: 835 surgeries in 800 patients were included in the analysis. Mean patient age was 66 years, 61.7% were female and 81.1% were prescribed mechanical prophylaxis in addition to warfarin. In the 90 days after surgery, there were 13 cases of symptomatic venous thromboembolism (1.6% of surgeries) which included 10 cases of pulmonary embolism (1.2% of surgeries). The incidence of clinically relevant bleeding during warfarin therapy was 0.8% and one death unrelated to bleeding or venous thromboembolism occurred.
Conclusions: Although warfarin produced low rates of clinically relevant bleeding and symptomatic venous thromboembolism, pulmonary embolism made up a greater proportion of events than anticipated. Low-intensity warfarin should be considered in future studies to identify the regimen that optimally balances risk of bleeding and symptomatic venous thromboembolism in a real world setting.

Introduction

Major orthopedic surgery presents a substantial risk of post-surgical venous thromboembolism (VTE) [1]. Rates of VTE have been reported as high as 60% in studies where screening for asymptomatic deep vein thrombosis (DVT) was undertaken, however symptomatic events occur much less frequently [1]. Without prophylaxis, the symptomatic VTE risk is estimated to be 4.3% during the initial 35 days following joint arthroplasty [1]. Due to this risk, thromboprophylaxis with antithrombotic medications is an established standard of practice [1,2].

Historically, consensus guidelines have not agreed on the most effective VTE prophylaxis regimen. The American Academy of Orthopaedic Surgeons (AAOS) recommend pharmacologic VTE prophylaxis following total hip arthroplasty (THA), but do not specify a preferred agent [2]. The 9th edition of the American College of Chest Physicians (ACCP) guidelines on VTE prevention in orthopedic surgery strongly recommends pharmacologic VTE prophylaxis over no therapy following THA (Grade 1B) and suggests a preference for low-molecular-weight heparin (LMWH) rather than other agents including vitamin K antagonists (VKA) (Grade 2C) [1]. Neither guideline specifies an international normalized ratio (INR) target for VKA therapy, though in past editions, the ACCP guideline recommended an INR of 2.0 to 3.0 while the AAOS guidelines supported a lower-intensity INR target of ≤ 2.0 [1–4]. Most contemporary studies evaluating postoperative VKA therapy have targeted the conventional INR range of 2.0 to 3.0 [5–10]. However, a recent survey of American Association of Hip and Knee Surgeon members found that among respondents prescribing warfarin thromboprophylaxis after THA, more than 90% target an INR lower than 2.0 to 3.0 due to perceived lower postoperative bleeding risk [11].

The few studies evaluating low-intensity warfarin following THA have limitations such as: abbreviated duration of warfarin

Abbreviations: THA, total hip arthroplasty; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist; AAOS, American Academy of Orthopaedic Surgeons; ACCP, American College of Chest Physicians; INR, International Normalized Ratio; KPCO, Kaiser Permanente Colorado; CPAAS, Clinical Pharmacy Anticoagulation and Anemia Service; EMR, electronic medical record; ED, emergency department; TJRR, total joint replacement registry; ICD-9, International Classification of Diseases, Ninth Revision; NSAID, non-steroidal anti-inflammatory drug.

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thromboprophylaxis, poorly described quality of anticoagulation control, and insufficient length of follow-up for VTE outcomes [12–15]. Extended follow-up after THA may be particularly important since post-surgical VTE risk persists up to 3 months, which is beyond the usual duration of prophylaxis [16,17]. Given the prevalent use of low-intensity warfarin thromboprophylaxis and limitations of pertinent studies, the purpose of this study was to quantify the incidence of symptomatic VTE, clinically relevant bleeding, and death in a cohort of real-world patients who received low-intensity warfarin after THA.

Materials and Methods

Study Design and Setting

This retrospective, cohort study was conducted at Kaiser Permanente Colorado (KPCO), an integrated healthcare delivery system providing care to over 500,000 patients in Colorado. Low-intensity warfarin (i.e., INR targeted to 1.5 to 2.5) is the preferred thromboprophylaxis strategy following THA at KPCO. Warfarin is started on postoperative day one and continued for up to six weeks or as determined by the orthopedic surgeon. Anticoagulant therapy at KPCO is managed by the Clinical Pharmacy Anticoagulation and Anemia Service (CPAAS). Pharmacists in CPAAS practice under collaborative drug therapy management agreements and are responsible for ordering relevant medications and labs, interpretation of lab results, warfarin dose titration, and coordination of follow-up INR monitoring [18]. Patient care activities are documented in an electronic medical record (EMR) and a computerized anticoagulation tracking system (DAWN AC; 4S Systems, Ltd., Cumbria, United Kingdom). All study activities were approved by the KPCO Institutional Review Board (IRB # CO-09-1344).

Study Population

The study cohort included patients who 1) had a THA between August 1, 2005 and July 31, 2009; 2) were aged ≥18 years at the time of THA; 3) had continuous KPCO membership in the 180 days prior and 90 days following the THA; and 4) received low-intensity warfarin (target INR 1.5 to 2.5) for postoperative VTE prevention. Patients with hip fracture, target INR range other than 1.5 to 2.5, and those receiving warfarin chronically for an indication other than postoperative VTE prevention were excluded.

Study Outcomes

The primary effectiveness outcome was symptomatic VTE (DVT and/or pulmonary embolism (PE) confirmed by compression ultrasound, ventilation/perfusion scanning, or computed tomography scanning). The primary safety outcome was clinically relevant bleeding. Death from any cause was also recorded. Symptomatic VTE events and all-cause mortality were included up to 90 days after THA. Bleeding outcomes were assessed only during warfarin therapy. Clinically relevant bleeding was defined as any unexpected post-surgical bleeding during the initial hospitalization or bleeding that resulted in hospitalization or an emergency department (ED) visit after discharge. Secondary outcomes included the incidence of major hemorrhage according to the International Society of Thrombosis and Haemostasis definition [19], postoperative infection, and time in therapeutic INR range measured according to the Rosendaal method [20].

Data Collection

The study cohort was identified using the Kaiser Permanente Total Joint Replacement Registry (TJRR); a clinically-validated registry containing over 90,000 joint replacement procedures [21]. Data for the TJRR are collected via queries of administrative databases, physician-completed forms, and manual medical record review and include information on patient demographics, medical history, thromboprophylaxis medications, and peri-operative outcomes.

An integrated, electronic KPCO membership database was queried to confirm membership eligibility and death during follow-up. Thromboembolic, bleeding, infection, and fatal events were identified from the TJRR and cross-verified with queries of KPCO electronic inpatient and outpatient databases by using predefined International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes (see Appendix). All VTE, bleeding and fatal events were confirmed through review of the EMR and Dawn-AC and adjudicated by two study team members (SEC and DMW) with disagreements decided by a 3rd reviewer (NPC).

Information on comorbidities (hypertension, diabetes mellitus, renal insufficiency, hepatic disease, previous VTE and cancer [solid tumor and metastatic]) in the 180 days prior to THA were identified via query of the KPCO medical office visits database using predefined ICD-9 codes. Target INR range, use of unfractionated heparin, LMWH or fondaparinux at the initiation of warfarin (bridge therapy), INR values, duration of thromboprophylaxis, and time above, below and within therapeutic INR range were obtained directly from the Dawn-AC database. Information on outpatient purchases of prescription nonsteroidal anti-inflammatory drugs (NSAIDs), estrogen, and corticosteroids during the 90 days prior to and 28 days following THA and unfractionated heparin, LMWH, or fondaparinux in the 90 days after THA was obtained from queries of the KPCO electronic pharmacy database and manual EMR review.

Data Analysis

All surgeries meeting inclusion and exclusion criteria were included; no a priori sample size calculation was performed. Patient characteristics were reported using descriptive statistics (means, medians, standard deviations, interquartile ranges, and proportions). Bleeding, VTE, death, and infection incident rates were calculated by dividing the number of specific incidences by the total count of included surgeries. The chi-square test of association and Fisher's exact test (as applicable) and Wilcoxon rank-sum tests were used to compare categorical and interval-level baseline characteristics, respectively, between patients who received bridge therapy and no bridge therapy.

Results

A total of 909 THAs were identified from the TJRR. Of these, 74 (8.1%) were excluded: 59 for chronic warfarin use other than for VTE prophylaxis, four did not receive warfarin due to a history of adverse effects, seven had target INR of 2 to 3 rather than 1.5 to 2.5, and one each for incorrect surgery date, fondaparinux monotherapy, lab monitoring unavailable, and warfarin treatment refused. Of the 7 patients treated to a target INR of 2 to 3, four had developed postoperative atrial fibrillation, two had prior history of VTE or known thrombophilia, and in one case the rationale was not identified. Thus, 835 THAs representing 800 patients were included in the analysis. No patient was lost to follow up.

Mean age was 66.2 years and hypertension was the most common comorbidity (20.6%) (Table 1). Twenty-seven percent of patients purchased a prescription NSAID during the study; all but 2 of these prescriptions were purchased prior to surgery. Most patients (81.1%) were prescribed mechanical VTE prophylaxis during hospitalization (Table 2). Bridge therapy with LMWH or fondaparinux during warfarin initiation was used in 5.2% of surgeries. There were no statistically significant differences in baseline characteristics of patients receiving and not receiving bridge therapy. The mean duration of thromboprophylaxis with warfarin was 40.1 days and the mean time-in-therapeutic range (INR 1.5 to 2.5) was 55.1%. Patients achieved an INR ≥ 1.5 by a median of 7 days (interquartile range 6 to 8 days).